

Applicants: Patrick Soon-Shiong et al.
Application No. 10/029,582

PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

AMENDMENT OF THE CLAIMS/LISTING OF CLAIMS

Please amend claim 53 as follows. This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Withdrawn): A microcapsule containing biologically active materials therein, the microcapsule comprising an ionically crosslinkable biocompatible gellable material, wherein at least the outer layer of said biocompatible gellable material is covalently crosslinked and optionally polyionically crosslinked, but not ionically crosslinked.
2. (Withdrawn): The microcapsule according to claim 1, wherein the core of said microcapsule is ionically crosslinked.
3. (Withdrawn): The microcapsule according to claim 2, wherein the core of said microcapsule is covalently crosslinked.
4. (Withdrawn): The microcapsule according to claim 1, wherein the core of said microcapsule is covalently crosslinked.
5. (Withdrawn): The microcapsule according to claim 4, wherein the core of said microcapsule is not ionically crosslinked.
6. (Withdrawn): The microcapsule according to claim 1, wherein the core of said microcapsule is not ionically crosslinked.
- 7.-38. (Cancelled)
39. (Withdrawn): A method of making a microcapsule containing biologically active materials therein and having substantially no ionic crosslinking in at least the outer layer thereof, said method comprising:subjecting a microcapsule which contains biologically active materials therein, wherein at least the outer layer thereof is ionically

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Application No. 10/029,582

PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

crosslinked, and wherein at least the outer layer thereof is covalently crosslinked and optionally polyionically crosslinked, to conditions sufficient to disrupt ionic crosslinking in at least the outer layer thereof, thereby forming a microcapsule having substantially no ionic crosslinking in at least the outer layer thereof.

40. (Withdrawn): A method of making a macrocapsule containing biologically active materials therein and having substantially no ionic crosslinking in at least the outer layer thereof, said method comprising: subjecting a macrocapsule which contains biologically active materials therein, optionally contained within at least one optionally present microcapsule, wherein at least the outer layer of the macrocapsule is ionically crosslinked, and wherein when microcapsules are not present, at least the outer layer of the macrocapsule is covalently crosslinked and optionally polyionically crosslinked, and when at least one microcapsule is present, at least the outer layer of the macrocapsule is covalently crosslinked or polyionically crosslinked or both covalently crosslinked and polyionically crosslinked, to conditions sufficient to disrupt ionic crosslinking in at least the outer layer thereof, thereby forming a macrocapsule having substantially no ionic crosslinking in at least the outer layer thereof.

41. (Withdrawn): A method of making a microcapsule containing biologically active materials therein, said method comprising simultaneously subjecting a droplet comprising a suspension of biologically active materials in a covalently crosslinkable carrier to conditions sufficient to prevent substantial dissociation thereof, and subjecting the droplet to conditions sufficient to induce substantial covalent crosslinking thereof, thereby forming the microcapsule.

42. (Withdrawn): The method of claim 41, wherein subjecting the droplet to conditions sufficient to prevent substantial dissociation thereof comprises contacting the droplet with a medium which is substantially immiscible with the droplet and which does not substantially inhibit the induction of covalent crosslinking.

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Application No. 10/029,582

PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

43. (Withdrawn): The method of claim 42, wherein the droplet is aqueous and the medium is selected from the group consisting of soybean oil, coconut oil, safflower oil, sunflower oil, and sesame oil.

44. (Withdrawn): The method of claim 42, wherein the droplet is aqueous and the medium comprises soybean oil.

45. (Withdrawn): The method of claim 42, wherein subjecting the droplet to conditions sufficient to induce substantial covalent crosslinking comprises irradiating the droplet with sufficient energy to induce photocrosslinking of the covalently crosslinkable carrier.

46. (Withdrawn): The method of claim 43, wherein subjecting the droplet to conditions sufficient to induce substantial covalent crosslinking comprises contacting the droplet with light from high pressure mercury lamps for a time sufficient to induce photocrosslinking of the covalently crosslinkable carrier.

47. (Withdrawn): A method of making a macrocapsule containing biologically active materials therein; said method comprising simultaneously subjecting a droplet comprising a suspension of a plurality of microcapsules containing the biologically active materials in a covalently crosslinkable carrier to conditions sufficient to prevent substantial dissociation thereof, and subjecting the droplet to conditions sufficient to induce substantial covalent crosslinking thereof, thereby forming the macrocapsule.

48. (Withdrawn): The method of claim 47, wherein subjecting the droplet to conditions sufficient to prevent substantial dissociation thereof comprises contacting the droplet with a medium which is substantially immiscible with the droplet and which does not substantially inhibit the induction of covalent crosslinking.

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PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

49. (Withdrawn): The method of claim 48, wherein the droplet is aqueous and the medium is selected from the group consisting of soybean oil, coconut oil, safflower oil, sunflower oil, and sesame oil.

50. (Withdrawn): The method of claim 48, wherein the droplet is aqueous and the medium comprises soybean oil.

51. (Withdrawn): The method of claim 48, wherein subjecting the droplet to conditions sufficient to induce substantial covalent crosslinking comprises irradiating the droplet with sufficient energy to induce photocrosslinking of the covalently crosslinkable carrier.

52. (Withdrawn): The method of claim 50, wherein subjecting the droplet to conditions sufficient to induce substantial covalent crosslinking comprises contacting the droplet with light from high pressure mercury lamps for a time sufficient to induce photocrosslinking of the covalently crosslinkable carrier.

53. (Currently amended): A microcapsule containing at least one cell aggregate therein, said microcapsule having a core which is not ionically crosslinked and an outer layer,

wherein said at least one cell aggregate is contained within the core;

wherein at least the outer layer of the microcapsule is covalently crosslinked, ~~polyionically crosslinked~~ or both covalently crosslinked and polyionically crosslinked, but not ionically crosslinked; and

wherein said covalently crosslinked outer layer is selected from the group consisting of covalently crosslinked polysaccharides, covalently crosslinked polyethylene glycols, covalently crosslinked polycationic materials, covalently crosslinked proteins, covalently crosslinked peptides, covalently crosslinked synthetic polymers, and mixtures of any two or more thereof.

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Application No. 10/029,582

PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

54. (Withdrawn): A macrocapsule containing at least one cell aggregate therein, said macrocapsule comprising a first biocompatible gellable material which is covalently crosslinkable and which contains at least one microcapsule therein, wherein each microcapsule comprises a second biocompatible gellable material which is ionically crosslinkable, wherein at least the outer layer of the macrocapsule is covalently crosslinked or polyionically crosslinked or both polyionically crosslinked and covalently crosslinked, wherein at least the outer layer of the microcapsule(s) is covalently crosslinked or polyionically crosslinked or both polyionically crosslinked and covalently crosslinked, and wherein the core of the microcapsule(s) is not ionically crosslinked and contains said at least one cell aggregate.

55. (Withdrawn): A macrocapsule containing at least one cell aggregate therein, said macrocapsule comprising a first biocompatible gellable material which is ionically crosslinkable and covalently crosslinkable and which optionally contains at least one microcapsule therein, wherein each microcapsule comprises a second biocompatible gellable material which is ionically crosslinkable, wherein at least the outer layer of the macrocapsule is covalently crosslinked or polyionically crosslinked or both polyionically crosslinked and covalently crosslinked, and wherein the core of the macrocapsule is not ionically crosslinked and contains said at least one cell aggregate.

56. (Withdrawn): A method of making a microcapsule containing at least one cell aggregate therein, said method comprising
subjecting a microcapsule comprising an ionically crosslinked biocompatible gellable material wherein at least the outer layer of the microcapsule is covalently crosslinked or polyionically crosslinked or both polyionically crosslinked and covalently crosslinked, wherein said microcapsule encapsulates at least one individual cell(s), to conditions sufficient to disrupt ionic crosslinking within the core of the microcapsule, thereby facilitating proliferation and/or aggregation of said individual cells to form at least one cell aggregate within the microcapsule.

Applicants: Patrick Soon-Shiong et al.
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PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

57. (Withdrawn): The method of claim 56, said method further comprising
subjecting the microcapsule to conditions sufficient to promote proliferation
of the at least one individual cell(s) after subjecting the microcapsule to conditions
sufficient to disrupt ionic crosslinking within the core of the microcapsule.
58. (Withdrawn): The method of claim 56, said method further comprising
subjecting the microcapsule to conditions sufficient to promote proliferation
of the at least one individual cell(s) before subjecting the microcapsule to conditions
sufficient to disrupt ionic crosslinking within the core of the microcapsule.
59. (Withdrawn): A method of making a macrocapsule containing at least one
cell aggregate therein, said method comprising
subjecting a macrocapsule comprising a first biocompatible gellable material
and at least one microcapsule therein, wherein at least the outer layer of the macrocapsule
is covalently crosslinked or polyionically crosslinked or both polyionically crosslinked and
covalently crosslinked, wherein each of the microcapsules comprises a second
biocompatible gellable material which is ionically crosslinked and which encapsulates at
least one individual cell, wherein at least the outer layer of the at least one microcapsule is
covalently crosslinked or polyionically crosslinked or both polyionically crosslinked and
covalently crosslinked, to conditions sufficient to disrupt ionic crosslinking within the core
of the at least one microcapsule, thereby facilitating proliferation and/or aggregation of said
at least one individual cell to form at least one cell aggregate within the core of the
microcapsule(s).
60. (Withdrawn): The method of claim 59, said method further comprising
subjecting the macrocapsule to conditions sufficient to promote proliferation
of said at least one individual cell after subjecting the macrocapsule to conditions sufficient
to disrupt ionic crosslinking within the core of the at least one microcapsule.
61. (Withdrawn): The method of claim 59, said method further comprising

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PATENT
Atty. Dkt. No. VIVOR1420-1
(073799-1107)

subjecting the macrocapsule to conditions sufficient to promote proliferation of said at least one individual cell before subjecting the macrocapsule to conditions sufficient to disrupt ionic crosslinking within the core of the at least one microcapsule.

62. (Withdrawn): A method of making a macrocapsule containing at least one cell aggregate therein, said method comprising

subjecting a macrocapsule comprising a first biocompatible gellable material and at least one individual cell encapsulated therein, optionally contained within at least one optionally present macrocapsule therein, wherein at least the outer layer of the macrocapsule is covalently crosslinked or polyionically crosslinked and covalently crosslinked, wherein each of the microcapsules comprises a second biocompatible gellable material which is ionically crosslinkable, to conditions sufficient to disrupt ionic crosslinking within microcapsule and at least the core of the macrocapsule, thereby facilitating proliferation and/or aggregation of said individual pancreatic islet cells to form at least one cell aggregate within the core of the macrocapsule.

63. (Withdrawn): The method of claim 62, said method further comprising
subjecting the macrocapsule to conditions sufficient to promote proliferation of the at least one individual cell after subjecting the macrocapsule to conditions sufficient to disrupt ionic crosslinking within the microcapsule and at least the core of the macrocapsule.

64. (Withdrawn): The method of claim 62, said method further comprising
subjecting the macrocapsule to conditions sufficient to promote proliferation of the at least one individual cell before subjecting the macrocapsule to conditions sufficient to disrupt ionic crosslinking within the microcapsule and at least the core of the macrocapsule.